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HUMORAL AND CELL-MEDIATED IMMUNE STATUS OF MICE EXPOSED TO TRANS-1,2-DICHLOROETHYLENE

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ABSTRACT

This study assessed possible adverse immunological effects of trans-1,2-dichloroethylene (DCE) on random-bred CD-1 mice following 14 and 90 days of exposure. A 14-day range-finding study was performed on male mice by gavage at doses 1/10 and 1/100 the LD50 (210 and 21 mg/kg). No alterations in either humoral or cell-mediated immunity were observed following this exposure. A 90-day study was conducted in which DCE was administered in the drinking water of male and female mice. The levels of DCE in the drinking water were calculated to deliver levels equivalent to, and higher than, those delivered for 14 days (17, 175, and 387 mg/kg for males and 23, 224, and 452 mg/kg for females). No changes were observed in the cell-mediated immune status of either sex or in the humoral immune status of females. However, a marked suppression in humoral immune status was observed in male mice exposed to all three levels of DCE, as indicated by a decreased ability of spleen cells to produce antibody against sheep erythrocytes (sRBC). Macrophage function was depressed only in females, as indicated by the decreased ability of thioglycollate-recruited peritoneal exudate cells (PEC) to phagocytize sRBC.

INTRODUCTION

Evaluation of the status of the immune system is assuming a significant role in the safety assessment of compounds. In the

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previous paper[1], many of the general toxicological parameters were described for CD-1 male and female mice exposed to DCE. The target of toxicity appeared to be the liver, as measured by glutathione levels and aniline hydroxylase activity.

This manuscript addresses the effects of DCE on the immune system. This work represents the first immunotoxicological evaluation of this compound and demonstrates the feasibility of such an investigation using a random-bred mouse. Although the preferred animal for toxicological investigations is the random-bred rat, we have chosen the random-bred mouse, since immunological assays have been standardized in the CD-1 mouse in this laboratory.

METHODS

Details of the methods for the immunotoxicological assays and historical controls have been fully described in the first article of this volume[2].

Exposure of Animals

Details concerning housing of the random-bred CD-1 mice and their exposure to DCE were given in the preceding paper[1]. The actual doses of DCE consumed as time-weighted averages of the three concentrations in the drinking water (0.1, 1.0, and 2.0 mg/ml) over 90 days were 17, 175, and 387 mg/kg for males and 23, 224, and 452 mg/kg for females. Details concerning fluid consumption during the drinking water study are also given in the preceding paper. In the 14-day gavage study, animals were sacrificed the day after the final gavage. For the drinking water study, animals were maintained on DCE until sacrificed.

Statistical Evaluation

If a one-way analysis of variance of the means showed treatment effects, a Duncan's Multiple Range Test was performed[3]. Values which differ from vehicle control at $p < 0.05$ were considered significant. Each of the values represent the mean ± SE.

RESULTS

Fourteen-Day Study

Humoral immune status of male mice following 14 days of gavage with DCE at doses 1/10 and 1/100 the LD50 (210 and 21 mg/kg) was evaluated by the ability of spleen cells from these mice to produce IgM antibody forming cells (AFC) against sRBC. As seen in Table 1, no significantly different changes from control were seen.

Cell-mediated immune status, as measured by the delayed-type hypersensitivity (DTH) response to sRBC (Table 2), was also unaffected in male mice exposed to DCE for 14 days.

TABLE 1
Humoral Immune Response to sRBC in Male CD-1 Mice Exposed for Fourteen Days by Gavage to DCE[a]

Exposure Group	Spleen Weight (mg)	AFC/Spleen ($\times 10^{-5}$)	AFC/10^6 Spleen Cells
Vehicle[b]	247 ± 20	3.98 ± 0.81	2236 ± 442
21 mg/kg	253 ± 30	4.26 ± 0.42	2761 ± 134
210 mg/kg	197 ± 12	2.84 ± 0.53	2052 ± 313

[a]Values represent mean ± SE of 9-10 mice per group.
[b]Vehicle = 10% emulphor

TABLE 2
Cell-Mediated Immune Response to sRBC in Male CD-1 Mice Exposed for Fourteen Days by Gavage to DCE[a]

Exposure Group	Stimulation Index
Vehicle[b]	3.28 ± 0.61
21 mg/kg	4.56 ± 0.37
210 mg/kg	3.50 ± 0.88

[a]Values represent mean ± SE of 10 mice per group. The unsensitized value = 1.77.
[b]Vehicle = 10% emulphor

Ninety-Day Study

Based on the results of the 14-day study, groups of male and female CD-1 mice were exposed to DCE in the drinking water at concentrations that would deliver equivalent amounts over a 24 hr period to those given in the 14-day gavage study. An additional group receiving a higher dose (1/5 the LD50) was added since the mice tolerated the lower doses so well in the 14-day range-finding study.

The three assays used to evaluate humoral immune status following 90 days of exposure were quantitation of spleen IgM AFC directed against sRBC on days 4 and 5 after antigen presentation, hemagglutination titers to sRBC, and spleen cell response to the B cell mitogen lipopolysaccharide (LPS).

When AFC were enumerated in males on the peak day of response (day 4), there was a significant decrease observed at all three dose levels of DCE (Table 3). When expressed as AFC per spleen basis, this decrease was only seen at the two highest doses, where both responses were 26% below control. No change in spleen weight was observed in these mice. On day 5, a depressed

TABLE 3
Humoral Immune Response to sRBC in CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Spleen Wt. (mg)	AFC/Spleen ($\times 10^{-5}$)	AFC/10^6 cells
Day 4		MALES	
Deionized Water	202 ± 30	4.48 ± 0.32	2200 ± 125
0.1 mg/ml	164 ± 13	3.28 ± 0.28*	2048 ± 152
1.0 mg/ml	178 ± 6	3.34 ± 0.39*	1625 ± 136*
2.0 mg/ml	173 ± 10	2.87 ± 0.37*	1618 ± 226*
		FEMALES	
Deionized Water	228 ± 13	4.38 ± 0.37	1765 ± 110
0.1 mg/ml	176 ± 11*	2.97 ± 0.49*	1478 ± 211
1.0 mg/ml	230 ± 12	4.51 ± 0.24	1967 ± 89
2.0 mg/ml	191 ± 13*	3.47 ± 0.50	1518 ± 184
Day 5		MALES	
Deionized Water	157 ± 10	1.34 ± 0.13	863 ± 64
0.1 mg/ml	134 ± 5	1.23 ± 0.10	841 ± 42
1.0 mg/ml	161 ± 10	1.14 ± 0.13	694 ± 64
2.0 mg/ml	146 ± 17	0.85 ± 0.11*	675 ± 57*
		FEMALES	
Deionized Water	201 ± 12	2.36 ± 0.14	1124 ± 51
0.1 mg/ml	217 ± 15	2.41 ± 0.37	1110 ± 109
1.0 mg/ml	230 ± 36	2.48 ± 0.31	947 ± 78
2.0 mg/ml	202 ± 11	2.16 ± 0.40	956 ± 149

[a]Values represent mean ± SE for 12 mice in the deionized water groups and 8 mice in the other groups. Values which differ significantly from control at $p < 0.05$ are noted by an asterisk.

response equivalent to that observed on day 4 in males was seen only at the highest dose level. The females responded normally on both days of measurement, except for the mice in the 0.1 mg/ml (lowest dose) group on day 4, where there was a 32% decrease in AFC response on a total spleen basis. It should be noted that the spleen size in this group of females was 23% smaller than control.

No changes were observed in hemagglutination titers of either sex (Table 4). Spleen lymphocyte responsiveness to LPS was also unaltered in the males (Table 5). However, the females exposed to the highest dose level of DCE did demonstrate a significantly enhanced spleen cell response (30 and 36%) to LPS at the lowest and highest concentrations of mitogen (Table 6). It should also be noted that baseline lymphocyte responsiveness in the absence of mitogen was significantly lower (32 and 36%) in females exposed to the two highest concentrations of DCE (Table 7).

Three assays used to evaluate the overall status of cellular immunity were the DTH response to sRBC, popliteal lymph node

TABLE 4
Hemagglutination Titers in CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Log_2 Titer	
	Males	Females
Deionized Water	8.48 ± 0.16	10.05 ± 0.08
0.1 mg/ml	8.77 ± 0.16	9.91 ± 0.12
1.0 mg/ml	8.44 ± 0.19	9.96 ± 0.15
2.0 mg/ml	8.54 ± 0.29	10.35 ± 0.18

[a]Values represent mean ± SE derived from 23 mice in control group and 11-6 mice in other groups.

TABLE 5
Lymphocyte Responsiveness to Con A and LPS Using Spleens from Male CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Con A cpm/5 x 10^5 cells	LPS cpm/5 x 10^5 cells
	1 µg/5 x 10^5 cells	1 µg/5 x 10^5 cells
Deionized Water	123954 ± 8510	37598 ± 4112
0.1 mg/ml	96452 ± 3428	27635 ± 3024
1.0 mg/ml	130609 ± 14598	46366 ± 6212
2.0 mg/ml	117877 ± 14822	38662 ± 5550
	5 µg/5 x 10^5 cells	5 µg/5 x 10^5 cells
Deionized Water	160613 ± 6271	50183 ± 5139
0.1 mg/ml	150496 ± 1372	46371 ± 8801
1.0 mg/ml	174288 ± 4212	56102 ± 6636
2.0 mg/ml	142562 ± 13127	62022 ± 9692
	10 µg/5 x 10^5 cells	20 µg/5 x 10^5 cells
Deionized Water	19529 ± 2450	45108 ± 4190
0.1 mg/ml	16755 ± 670	35453 ± 2921
1.0 mg/ml	13683 ± 2032	49625 ± 5999
2.0 mg/ml	12464 ± 1983	55175 ± 9174

[a]Values represent mean cpm's ± SE derived from 2-9 mice per group.

TABLE 6
Lymphocyte Responsiveness to Con A and LPS Using Spleens from Female CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Con A cpm/5 x 10^5 cells	LPS cpm/5 x 10^5 cells
	1 µg/5 x 10^5 cells	1 µg/5 x 10^5 cells
Deionized Water	131551 ± 11495	35121 ± 1212
0.1 mg/ml	152790 ± 15230	40489 ± 3488
1.0 mg/ml	148374 ± 10561	34951 ± 2577
2.0 mg/ml	123274 ± 5214	47952 ± 2729*
	5 µg/5 x 10^5 cells	5 µg/5 x 10^5 cells
Deionized Water	170588 ± 9535	50314 ± 2729
0.1 mg/ml	180035 ± 1318	51850 ± 6326
1.0 mg/ml	162040 ± 14510	45191 ± 3847
2.0 mg/ml	145580 ± 5829	58141 ± 3040
	10 µg/5 x 10^5 cells	20 µg/5 x 10^5 cells
Deionized Water	10206 ± 321	42915 ± 2027
0.1 mg/ml	10681 ± 147	45409 ± 8166
1.0 mg/ml	10334 ± 3068	41317 ± 2843
2.0 mg/ml	8196 ± 1035	55748 ± 4294*

[a]Values represent mean cpm's ± SE derived from 2-7 mice per group. Values which differ significantly from control at $p < 0.05$ are noted by an asterisk.

TABLE 7
Lymphocyte Proliferation in the Absence of Mitogen Using Spleens from CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	MALES cpm/5 x 10^5 cells	FEMALES cpm/5 x 10^5 cells
Deionized Water	4640 ± 732	6294 ± 124
0.1 mg/ml	3556 ± 363	4711 ± 437
1.0 mg/ml	5402 ± 606	4300 ± 629*
2.0 mg/ml	5346 ± 210	4056 ± 491*

[a]Values represent mean ± SE derived from 2-9 mice per group. Values which differ significantly from control at $p < 0.05$ are noted by an asterisk.

proliferation in response to sRBC, and spleen cell response to Concanavalin A (Con A).

Male mice exposed to DCE for 90 days did not show changes in either the DTH or popliteal lymph node proliferation response to sRBC (Tables 8 and 9), while the females exposed to 1.0 mg/ml had a slight increase in the DTH response. No alterations in spleen lymphocyte response to Con A were seen in either sex (Tables 5 and 6).

The number of PEC recruited, the number of PEC able to adhere to plastic, the chemotactic ability of the recruited cells, and the phagocytic ability of the adherent cells were assessed.

Mice of either sex exposed to DCE showed no significant alterations in the number of recruitable PEC, the number of cells that could adhere to plastic, or the phagocytic activity of the adherent cells. In the males, there were no DCE-related

TABLE 8
Cell-Mediated Immune Response to sRBC in CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	MALES Stimulation Index	FEMALES Stimulation Index
Deionized Water	3.25 ± 0.32	2.93 ± 0.28
0.1 mg/ml	3.30 ± 0.50	3.42 ± 0.33
1.0 mg/ml	3.68 ± 0.39	3.82 ± 0.26*
2.0 mg/ml	3.34 ± 0.51	3.69 ± 0.33

[a]Values represent mean ± SE derived from 16-19 mice per group. The unsensitized value was 1.71 for males and 1.65 for females. Values which differ significantly from control at $p < 0.05$ are noted by an asterisk.

changes in the chemotactic ability of PEC. One significant chemotactic effect was seen in female mice at the 1.0 mg/ml exposure level. However, this decrease may not be related to chemical exposure, since it was only observed at the middle dose (data not shown).

The functional ability of the fixed macrophages of the reticuloendothelial system (RES) was assessed by measuring the vascular clearance rate and tissue uptake of ^{51}Cr-labeled sRBC. The males demonstrated no changes in RES activity (Table 10). Females exposed to the highest level of DCE demonstrated a slight decrease in the percent uptake of radiolabel into the thymus (Table 11). It should be noted that the thymuses of these mice were smaller; therefore, no change from control was measured when calculations were made on a specific activity basis, i.e., cpm/mg tissue.

The ability of bone marrow cells from DCE exposed mice for 90 days to incorporate ^{125}I-IUdR was essentially unaffected

TABLE 9
Popliteal Lymph Node Proliferation in CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Males	Females
Deionized Water	5.12 ± 0.64	9.89 ± 0.80
0.1 mg/ml	4.75 ± 0.40	8.48 ± 1.20
1.0 mg/ml	5.47 ± 0.64	10.77 ± 1.27
2.0 mg/ml	5.06 ± 0.61	9.93 ± 0.71

[a]Values represent mean ± SE derived from 11-20 mice per group.

TABLE 10
Functional Activity of the Reticuloendothelial System in Male CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Body Wt. (g)	Phagocytic Index	Organ	% Uptake[b]	cpm/mg[c]
Deionized Water	39.5 ± 0.8	0.14 ± 0.02	Liver	49.5 ± 2.2	239 ± 21
			Spleen	5.8 ± 0.8	345 ± 51
			Lungs	1.01 ± .11	31 ± 4
			Thymus	.009 ± .001	3 ± 1
			Kidneys	2.5 ± 0.2	31 ± 2
0.1 mg/ml	39.7 ± 0.8	0.11 ± 0.02	Liver	49.6 ± 3.2	235 ± 12
			Spleen	7.6 ± 1.0	417 ± 56
			Lungs	.94 ± .17	28 ± 6
			Thymus	.008 ± .001	3 ± 1
			Kidneys	2.2 ± 0.4	28 ± 5
1.0 mg/ml	41.0 ± 1.1	0.13 ± 0.02	Liver	50.3 ± 3.9	217 ± 18
			Spleen	6.8 ± 1.1	356 ± 73
			Lungs	.83 ± .32	19 ± 7
			Thymus	.011 ± .002	3 ± 1
			Kidneys	2.0 ± 0.3	25 ± 3
2.0 mg/ml	41.4 ± 0.9	0.14 ± 0.02	Liver	51.0 ± 4.2	219 ± 14
			Spleen	6.3 ± 1.0	329 ± 70
			Lungs	.85 ± .15	29 ± 10
			Thymus	.010 ± .002	4 ± 1
			Kidneys	2.1 ± 0.3	28 ± 4

[a]Values represent mean ± SE derived from 7-10 mice per group.
[b]% Uptake = cpm in organ/cpm injected x 100
[c]cpm/mg = cpm/mg of organ

TABLE 11
Functional Activity of the Reticuloendothelial System in Female CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	Body Wt. (g)	Phagocytic Index	Organ	% Uptake[b]	cpm/mg[c]
Deionized Water	31.5 ± 0.5	0.07 ± 0.02	Liver	56.4 ± 1.9	247 ± 8
			Spleen	7.4 ± 1.1	299 ± 53
			Lungs	.93 ± .24	26 ± 7
			Thymus	.012 ± .001	4 ± 1
			Kidneys	1.9 ± 0.2	30 ± 3
0.1 mg/ml	33.6 ± 1.2	0.06 ± 0.03	Liver	54.6 ± 4.4	264 ± 30
			Spleen	9.7 ± 1.4	409 ± 74
			Lungs	.80 ± .24	26 ± 8
			Thymus	.012 ± .001	5 ± 2
			Kidneys	1.9 ± 0.3	27 ± 4
1.0 mg/ml	32.4 ± 1.2	0.07 ± 0.01	Liver	56.6 ± 4.1	255 ± 23
			Spleen	6.3 ± 0.8	397 ± 104
			Lungs	.69 ± .10	24 ± 5
			Thymus	.008 ± .002	7 ± 2
			Kidneys	2.1 ± 0.2	38 ± 8
2.0 mg/ml	32.3 ± 1.1	0.08 ± 0.03	Liver	52.1 ± 2.6	234 ± 16
			Spleen	7.6 ± 1.4	479 ± 81
			Lungs	1.17 ± .32	36 ± 8
			Thymus	.007 ± .001*	4 ± 1
			Kidneys	2.1 ± 0.3	34 ± 4

[a]Values represent mean ± SE derived from 8-12 mice per group. Values which differ significantly from control are noted by an asterisk.
[b]% Uptake = cpm in organ/cpm injected x 100
[c]cpm/mg = cpm/mg of organ

(Table 12). There was a slight increase in DNA synthesis following 60 min of incubation with ^{125}I-IUdR in females exposed to the highest level of DCE; however, this increase was not seen after 120 min of incubation.

DISCUSSION

The objective of this study was to evaluate any alterations produced in the immune system of random-bred CD-1 mice exposed

TABLE 12
Bone Marrow DNA Syntnesis in CD-1 Mice Exposed to DCE in the Drinking Water for 90 Days[a]

Exposure Group	cpm/6 x 10^5 cells			
	MALES		FEMALES	
	60 min	120 min	60 min	120 min
Deionized Water	15265 ± 800	28498 ± 895	16220 ± 999	28202 ± 1546
0.1 mg/ml	13327 ± 1098	29078 ± 1824	15092 ± 1000	25634 ± 1320
1.0 mg/ml	15117 ± 1047	29842 ± 1590	13668 ± 538	34583 ± 2728
2.0 mg/ml	14192 ± 1431	27625 ± 927	20390 ± 2556*	31402 ± 3484

[a]Values represent mean cpm's ± SE derived from 6-12 mice per group. Values which differ significantly from control at $p < 0.05$ are noted by an asterisk.

to DCE for 14 or 90 days. A standard toxicological profile on this compound was previously presented[1], in which the most notable findings were decreased glutathione levels in males and decreased aniline hydroxylase activity in females. This was in accordance with previous investigations in which the mixed function oxidase system was inhibited by 1,2-DCE[4]. It has also previously been determined that at least one component of the immune system, the Kupffer cell of the liver, undergoes slight to severe fatty generation due to the 1,2-DCE exposure[5].

It is evident from the present study that, although DCE has effects upon the immune system, these effects were often not dose-dependent, did not coincide with tests measuring similar parameters, and did not occur in both sexes. No alteration in either humoral or cell-mediated immunity was observed in male mice exposed by daily gavage for 14 days to doses 1/10 and 1/100

the LD50 (210 and 21 mg/kg). However, there were some immunological changes that occurred following 90 days of exposure to the compound in the drinking water. In males, the number of IgM AFC was significantly decreased at all dose levels. This decrease was not severe enough to depress the functional ability of the humoral immune system, as evidenced by normal hemagglutination titers and spleen cell response to LPS. The females exposed to DCE for 90 days showed a change in humoral immunity in that responsiveness to LPS was enhanced in the high dose group. It is questionable whether or not this has any true biological significance, since the increases were not very great and did not occur at the optimum LPS concentration.

The cell-mediated immune system was not affected by exposure to DCE as evaluated by the DTH response, proliferation of popliteal lymph node cells, and spleen cell responsiveness to Con A.

The fixed macrophage system, as evaluated by the functional activity of the RES, was intact and essentially unchanged in both sexes of mice following 90 days of exposure to DCE.

In conclusion, the immune system of random-bred CD-1 mice does not appear to be overly sensitive to the effects of DCE. The few effects which were seen were probably the result of general toxicity as opposed to specific target organ toxicity.

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